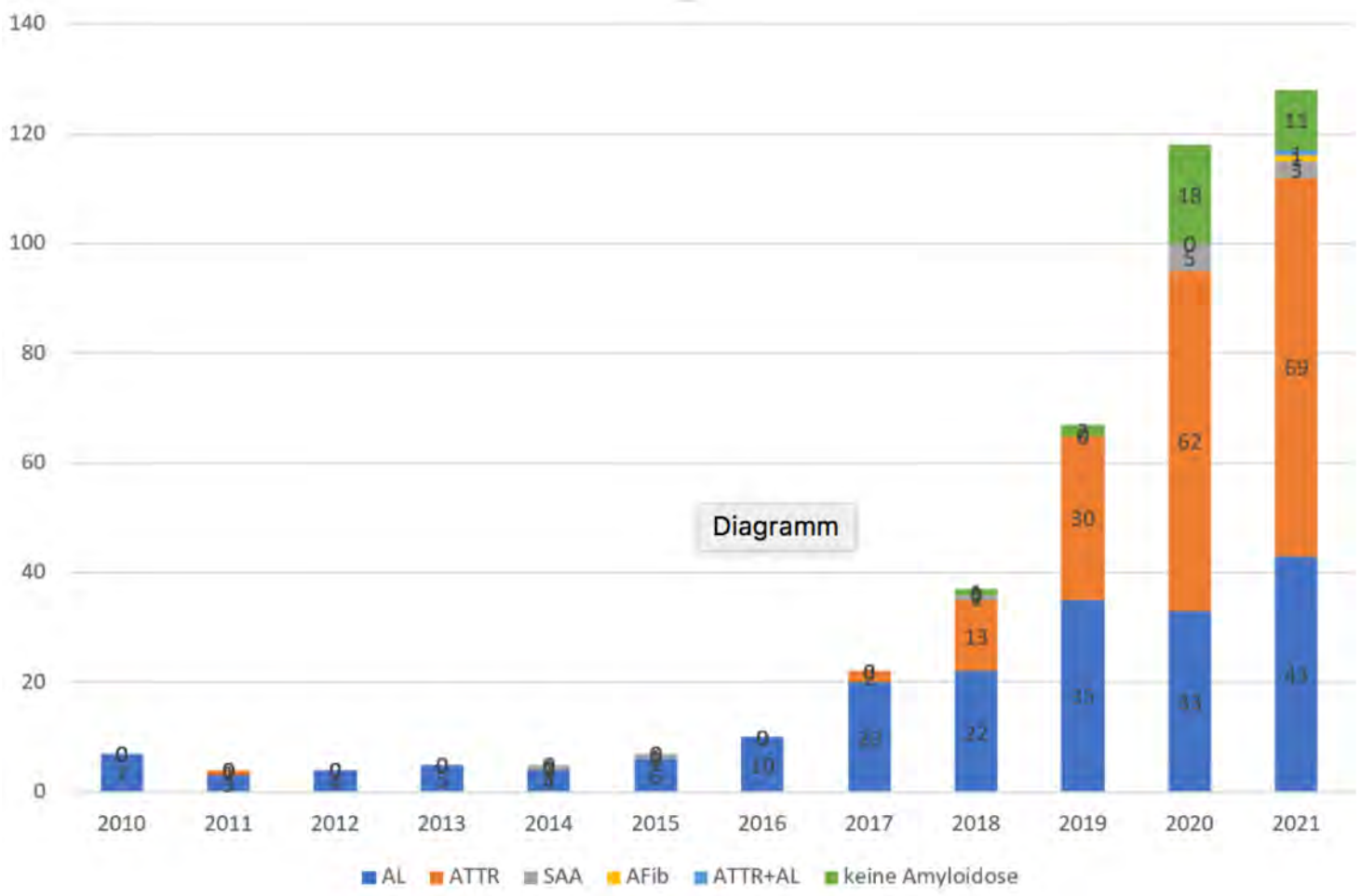
Ursachen/Diagnostik von Amyloidosen

Alexander Carpinteiro
Institut für Molekularbiologie
Klinik für Hämatologie
Universitätsklinik Essen

Erstvorstellungen Amyloidose am UK-Essen

Interdisziplinäres Netzwerk zur Behandlung von Amyloidosen am UK-Essen

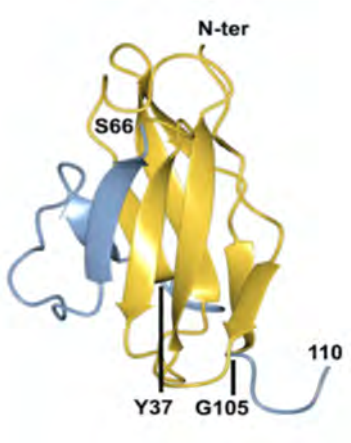


Hämatologie und Stammzelltransplantation
Kardiologie
Neurologie
Gastroenterologie
Nephrologie
Nuklearmedizin
Radiologie

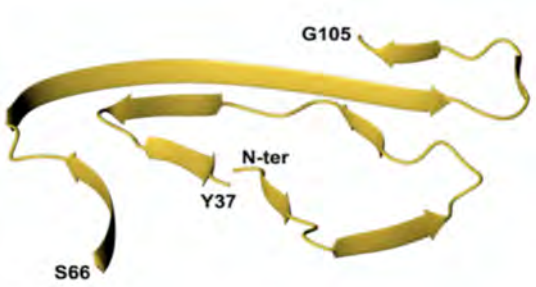
Amyloidose-Board alle 2 Wochen

- Besprechung der neuen Patienten und „Problemfälle“
- Demonstration von Bildgebung
- Besprechung von wissenschaftlichen Projekten

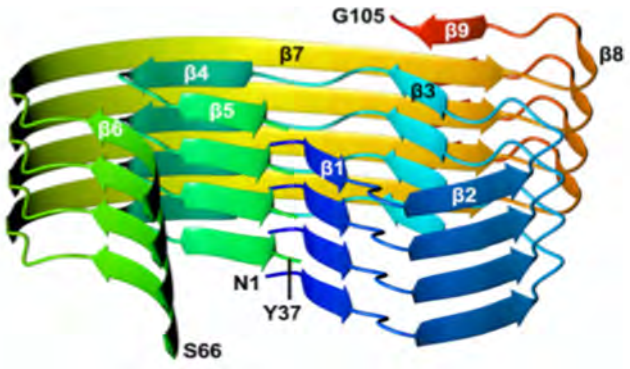
Amyloidosen sind Eiweiß-Ablagerungs-Erkrankungen



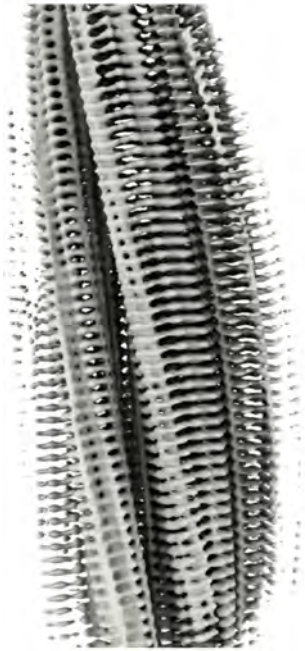
Ursprüngliches Eiweiß (Protein)



„Falsch“ gefaltetes Protein, ß-Faltbalttstruktur



Amyloid



3 D Rekonstruktion aus Cryo-EM

Swuec et al. 2019, Nature communications
Swuec et al. 2020, ISA Poster PM 014

Es gibt viele Amyloidosen!

	Acquired or hereditary	Patients seen at UK-NAC (%; n=5100)	Underlying disorder	Precursor protein	Organ involvement					Treatment	Treatment target
					Heart	Kidneys	Liver	PN (AN)	Other		
AL	Acquired	4067 (68%)	Plasma cell dyscrasia	Monoclonal immunoglobulin light chain	+++	+++	++	+(+)	Soft tissue gastrointestinal	Chemotherapy or ASCT	dFLC <40 mg/L
AA	Acquired	633 (12%)	Inflammatory disorders (RA, JIA, IVDU, FPS)	SAA	–/+ (late)	+++	+(late)	–	Gastrointestinal (late)	Suppression of inflammation	SAA <4 mg/L
ATTR	Acquired	168 (3·2%)	..	Wild-type TTR	+++	–	–	–	Carpal tunnel syndrome	Supportive	Optimum control of heart failure
	Hereditary	339 (6·6%)	Mutations in TTR gene	Abnormal TTR	++	–	–	+++ (+++)	–	Liver transplant (younger patients with V30M-related ATTR), diflunisal, (doxycycline/ TUDCA) Supportive	Optimum control of congestive heart failure and symptoms of PN/AN
AFib	Hereditary	87 (1·7%)	Mutations in fibrinogen α-chain gene	Abnormal fibrinogen	–	+++	–/+	–	–	Supportive, organ transplant	Preserve renal function
ALect2	Acquired	16 (0·3%)	Uncertain	Lect2	–	+++	++	–	–	Supportive	Preserve renal function
AApoA1	Hereditary	40 (0·8%)	Mutations in apolipoprotein A1 gene	Abnormal ApoA1	+	++	++	+/–(–)	Testis	Supportive, organ transplant	Preserve renal function
ALys	Hereditary	17 (0·3%)	Mutations in lysozyme gene	Abnormal lysozyme	–	+	++	–	Gastrointestinal or skin	Supportive	..
AGel	Hereditary	4 (0·1%)	Mutations in gelsolin gene	Abnormal gelsolin	–	-/+	–	++(–) cranial	–	Supportive	..
Aβ2M	Acquired or hereditary	93 (1·8%)	Long-term dialysis	Aβ2M	–	–	–	–(+*)	Carpal tunnel syndrome, arthropathy	Supportive, renal transplant	..

Aβ2M=β2-microglobulin-related. AFib=fibrinogen A α-chain. AGel=gelsolin amyloid. AL=amyloid light chain. ALect2=leucocyte cell-derived chemotaxin 2. ALys=lysozyme amyloid. AN=autonomic neuropathy. ASCT=autologous stem cell transplant. ATTR=amyloid transthyretin. dFLC=difference between involved and uninvolved free light chain. FPS=familial periodic fever syndromes. IVDU=intravenous drug abuse. JIA=juvenile inflammatory arthritis. PN=peripheral neuropathy. RA=rheumatoid arthritis. SAA=serum amyloid A. TTR=transthyretin. TUDCA=tauro-ursodeoxycholic acid. UK-NAC=UK National Amyloidosis Centre. *AN only in familial Aβ2M amyloidosis.[8] + indicates relative frequency: +++ very common, ++ common; + less common; –/+ rare; – not applicable or does not occur in this condition. (drug)=undergoing clinical trials. AA=amyloid A. AApoA1= apolipoprotein A1 amyloid.

Table 1: **Characteristics of the common types of amyloidosis**

Wann entsteht eine Amyloidose?

1. Mutation, Fehlfaltung => angeborene Amyloidosen

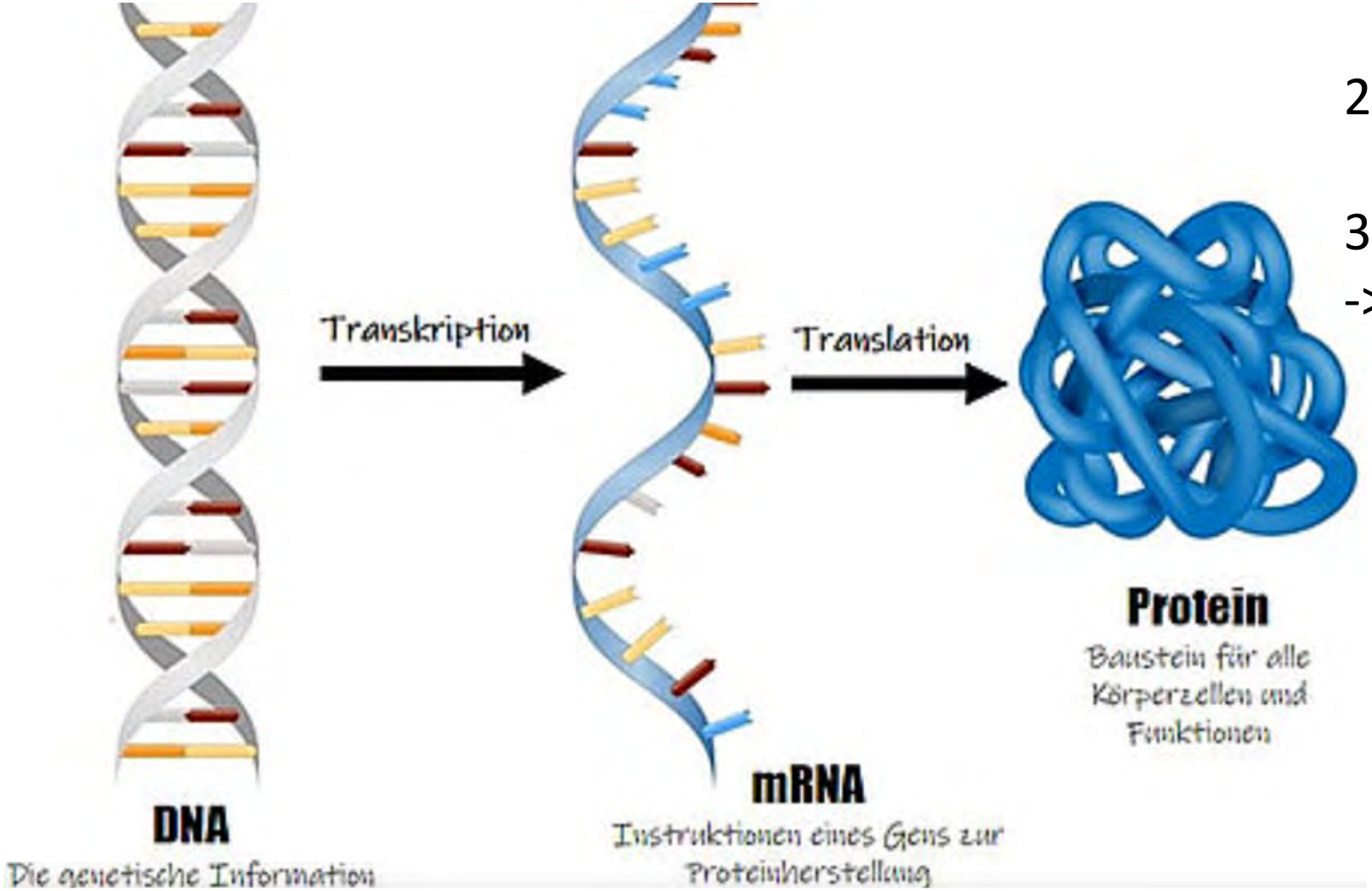
2. Normales Protein, aber viel zu viel davon => erworbene Amyloidosen

Wechelaker et al 2016 Lancet

Mutationen sind oft die Ursache für fehlgefaltete Eiweiße

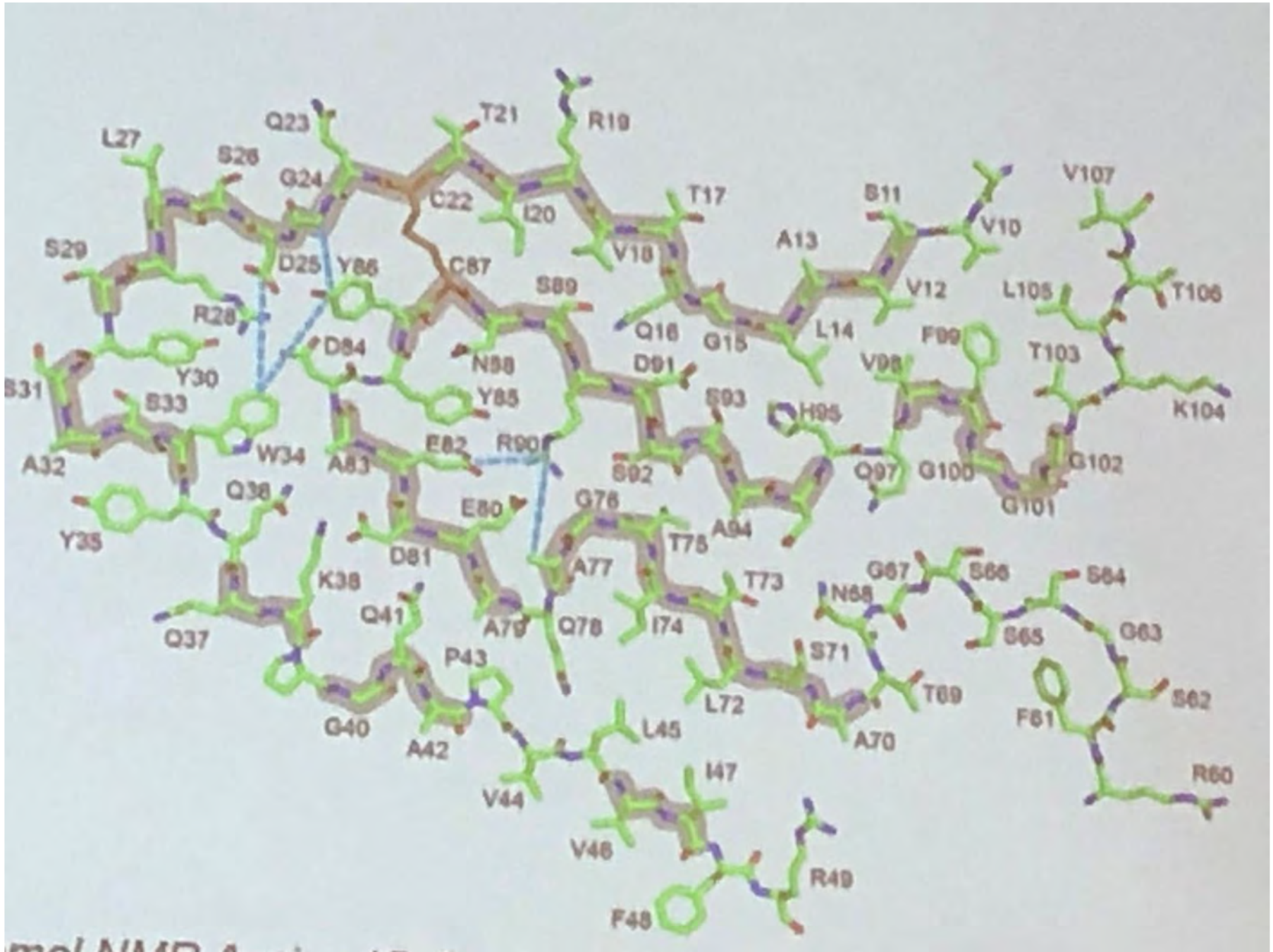
Nukleinsäuren

Adenin A
Cytosin C
Guanin G
Thymin T

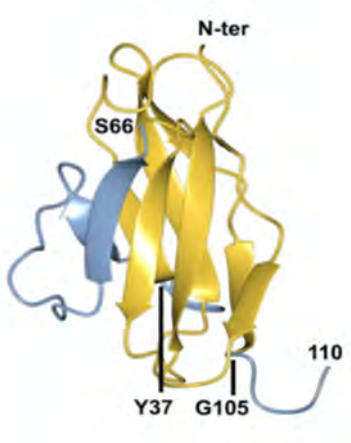


20 Aminosäuren

3 Buchstabencode
-> 1 Aminosäure


Q23
T21
R19
L27
S26
G24
C22
I20
T17
S11
V107
V10
A13
V18
S29
D25
Y86
C87
S89
V12
L105
T106
R28
Q16
G15
L14
F99
T103
D84
N88
D91
V98
Y30
S31
S33
Y85
S93
H95
K104
W34
E82
R90
A32
A83
S92
Q97
G100
G102
Q36
E80
G76
G101
Y35
A94
T75
D81
A77
G67
S66
S64
K38
T73
N68
Q41
I74
S65
G63
Q37
A79
Q78
S71
P43
T69
S62
L72
F61
G40
L45
A70
A42
I47
R60
V44
V46
R49
F48

Amyloidosen sind Eiweiß-Ablagerungs-Erkrankungen



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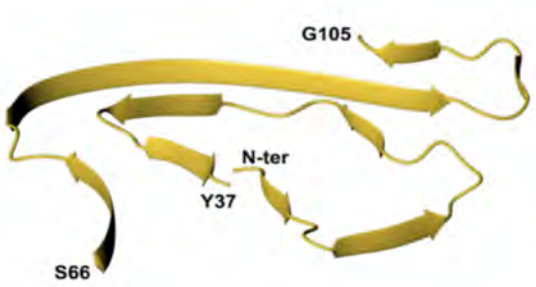
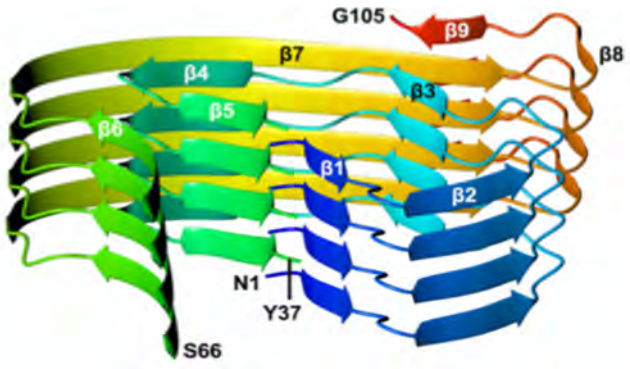
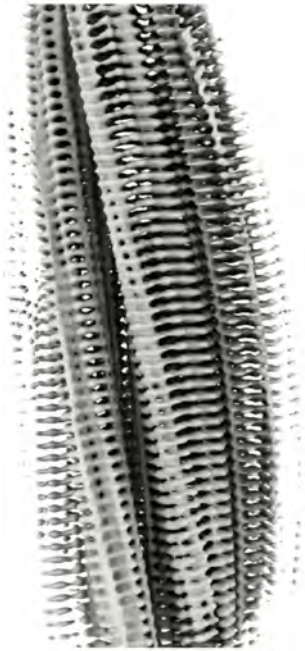


„Falsch“ gefaltetes Protein, ß-Faltbalttstruktur



Amyloid



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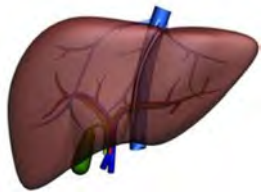
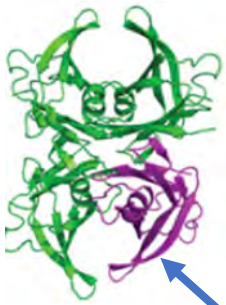
ATTR – Amyloidose ….Transthyretin





Tetramer dissociation

Point-mutation or wt

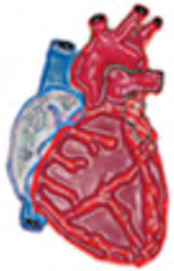
monomer misfolding

wtTTR

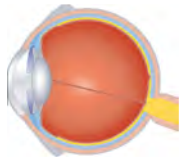
SAP

aggregation and organ targeting

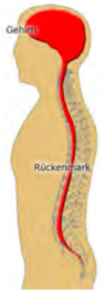
mTTR

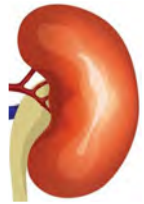


cardiac



occular and CNS



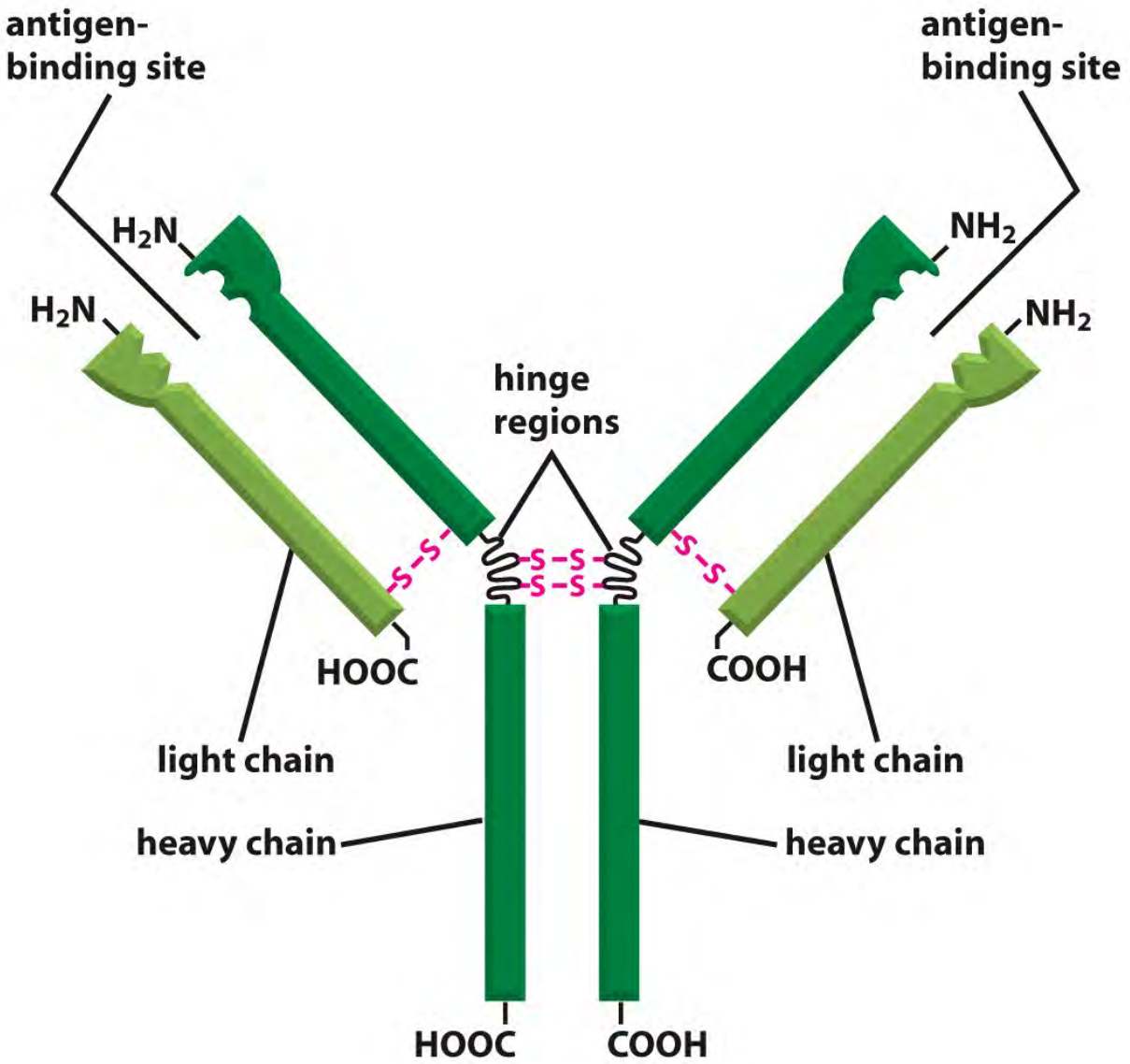


kidney

peripheral neuropathy

Quintas et al. JBC 2001, Marcoux et al. EMBO Mol Med 2015, Quarta et al. NEJM 2015

Antikörper


antigen-
binding site
antigen-
binding site
H_2N
H_2N
NH_2
NH_2
hinge
regions
S–S
S–S
S–S
S–S
HOOC
COOH
light chain
light chain
heavy chain
heavy chain
HOOC
COOH

Antikörpervielfalt

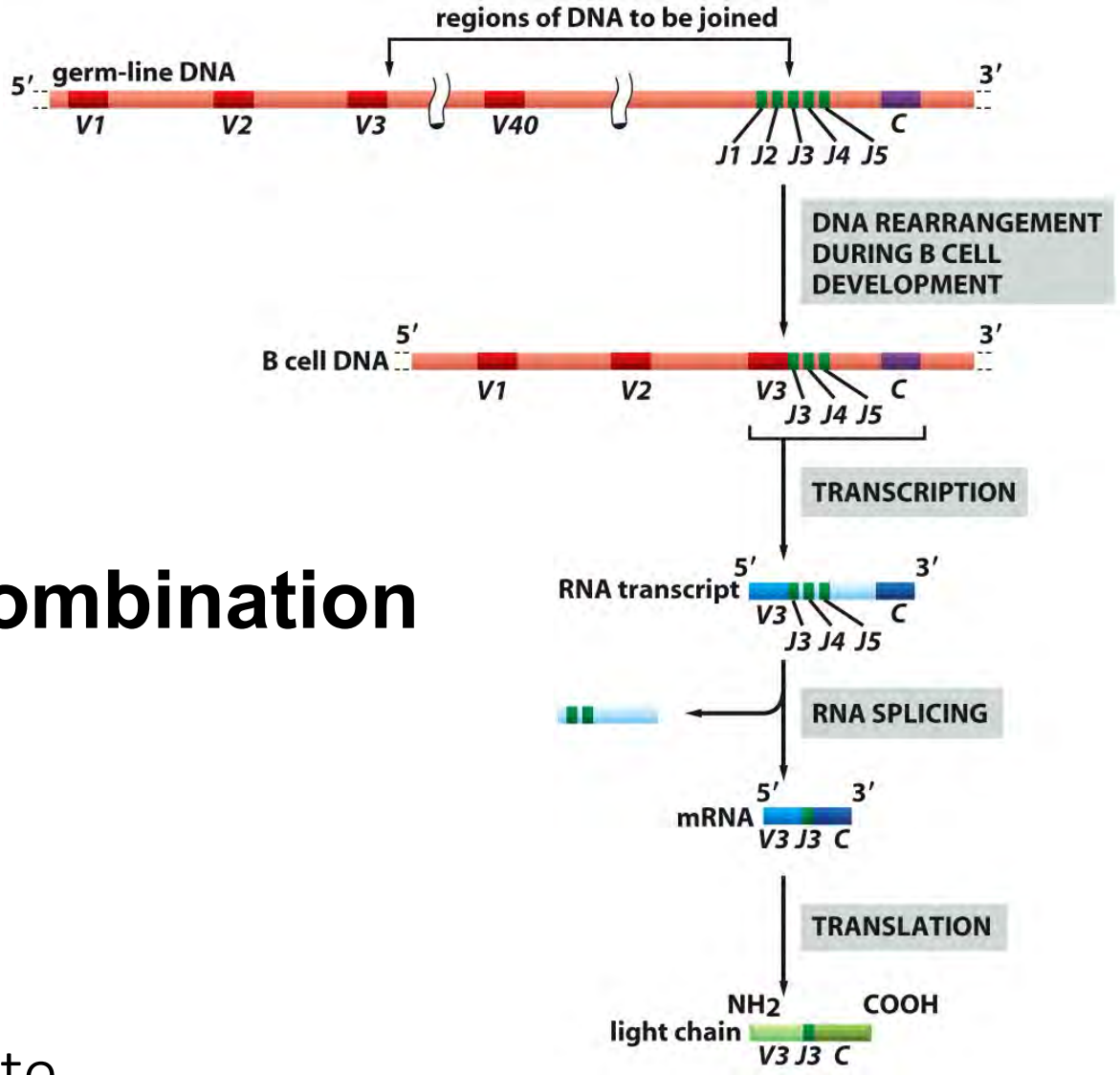
fast alle Substanzen können Gegenstand einer Antikörper-Antwort sein

→ Mehr als **$1x10^{12}$ verschiedene Antikörper** (> 1.000.000.000.000) sind möglich

.... Es gibt aber nur 25.000 Gene....

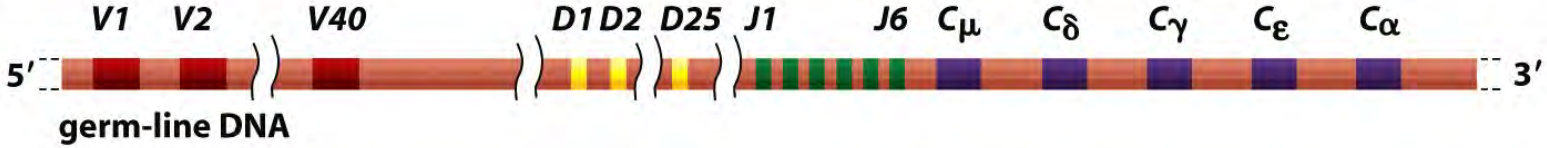
Wie können 25.000 Gene über 10^{12} unterschiedliche Proteine kodieren?

Leichte Kette

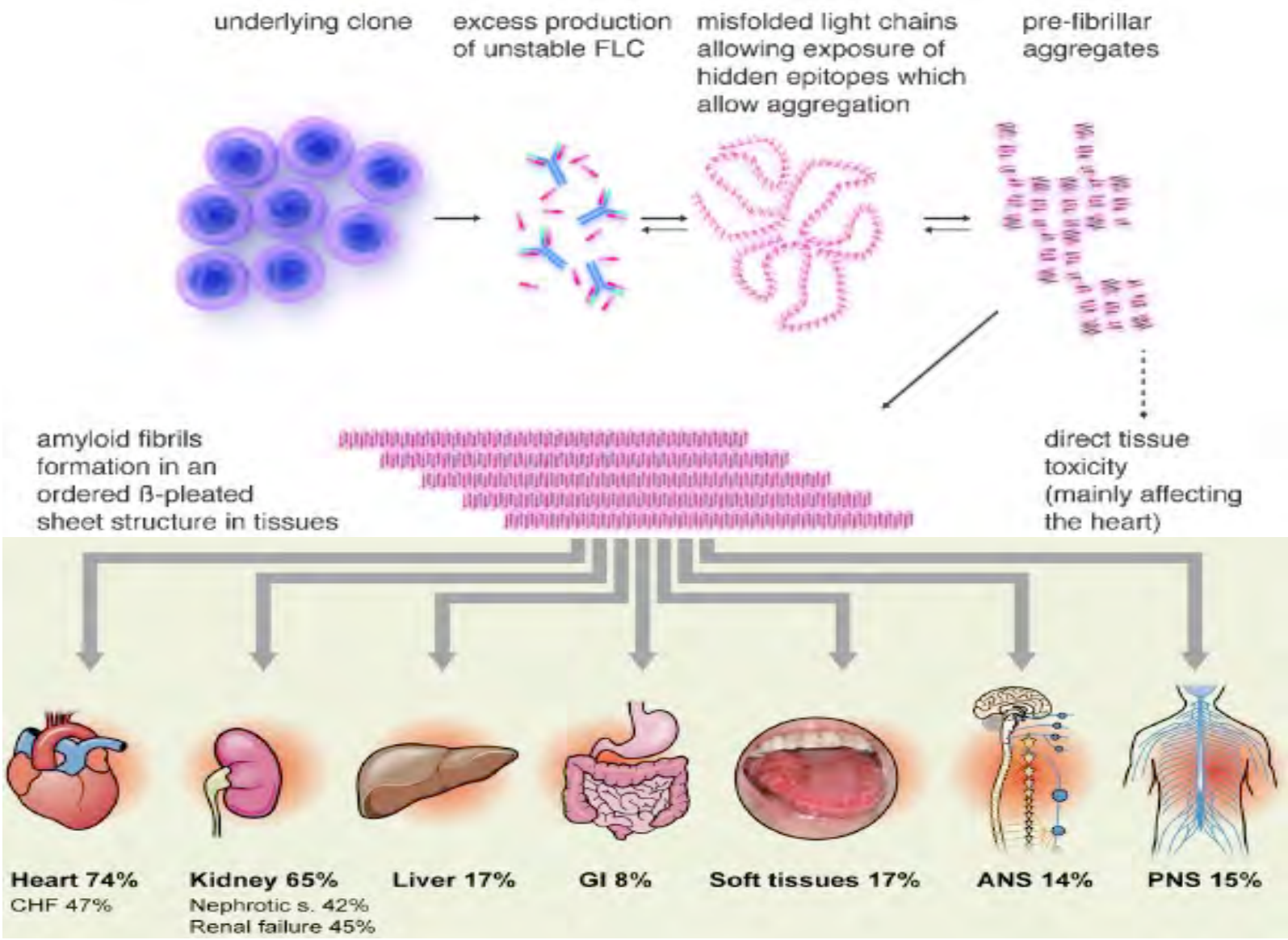


V(D)J – Rekombination

Schwere Kette

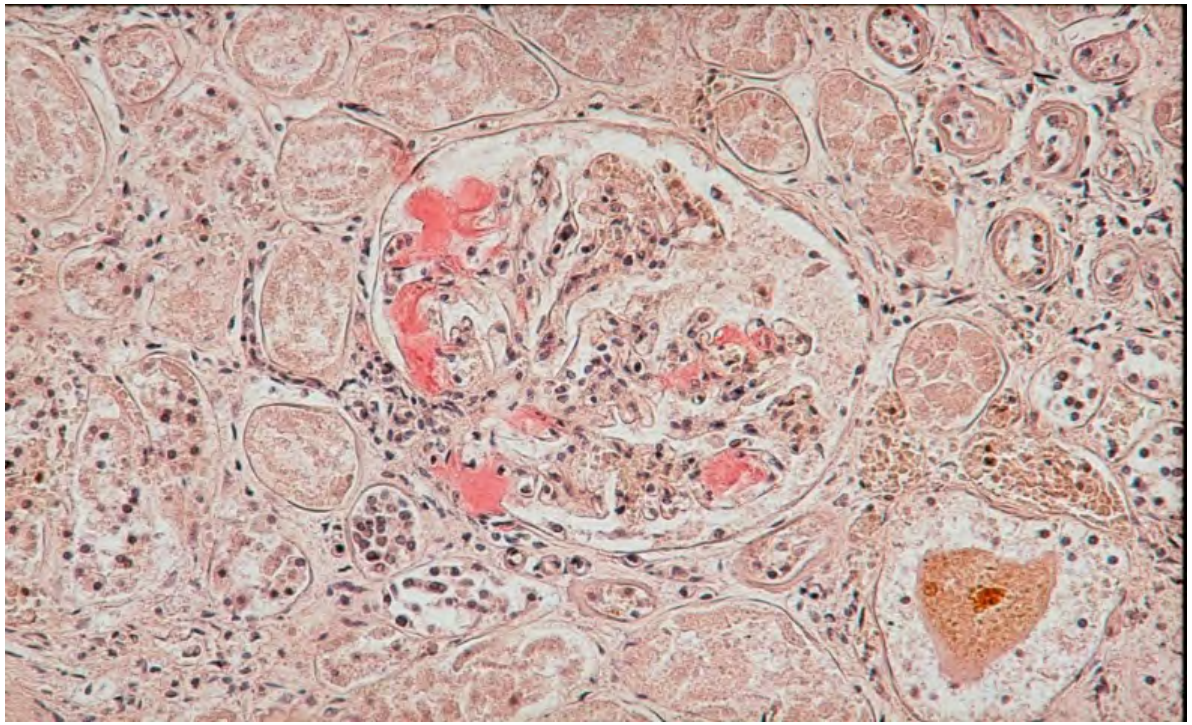


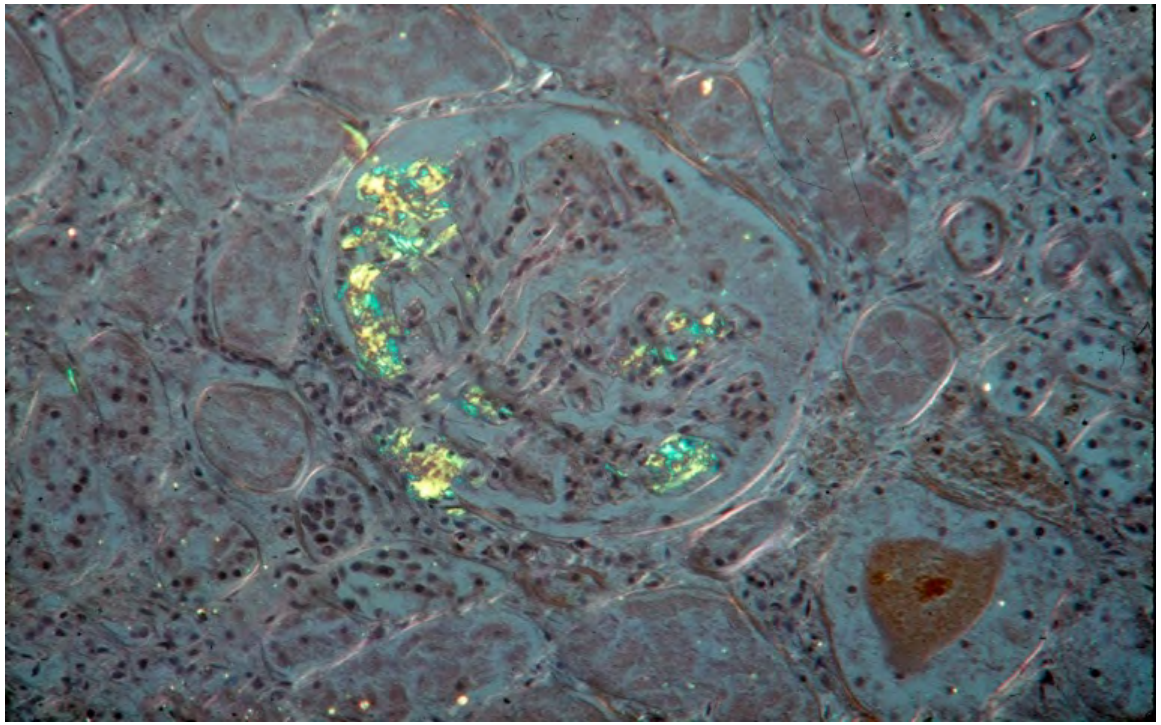
AL Amyloidose….. Leichtketten



Mahmood et al. 2013 Haematologica und Merlini et al., Blood 2012

Amyloidose ist eine histologische Diagnose





Eine Ausnahme!!! Szintigrafie bei ATTR Amyloidose mit Herzbefall

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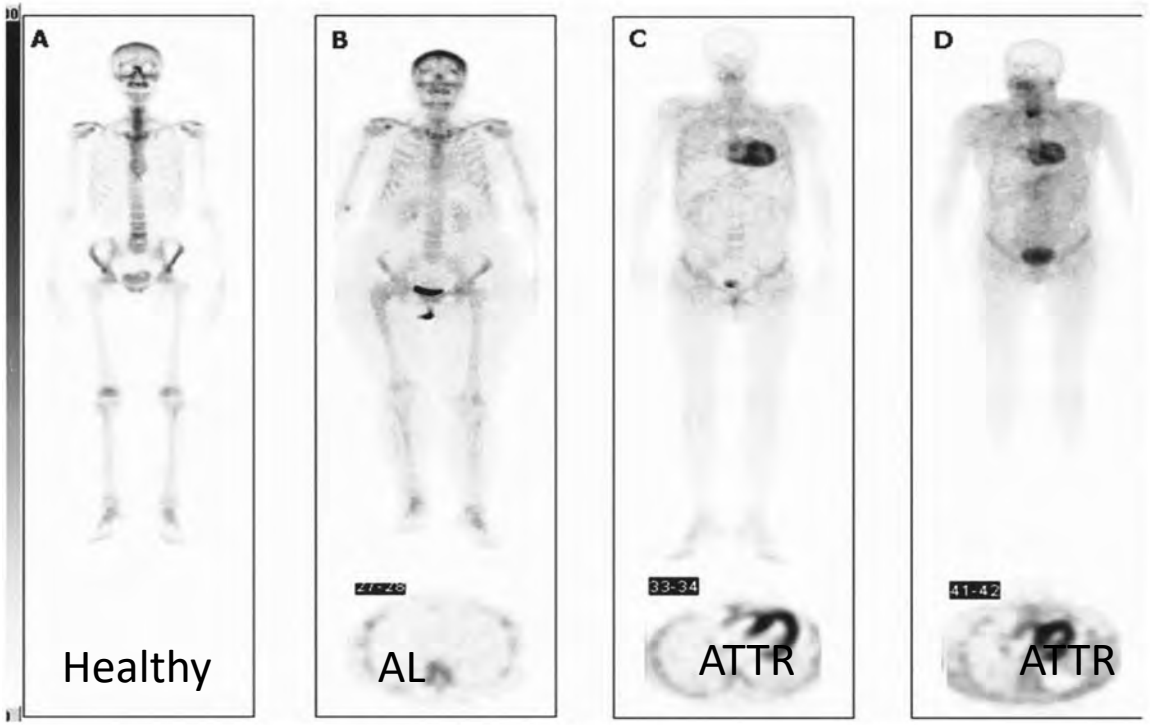
Cardiac Imaging

Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using ^{99m}Tc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy

Enrica Perugini, MD,* Pier Luigi Guidalotti, MD,† Fabrizio Salvi, MD,‡ Robin M. T. Cooke, MA,* Cinzia Pettinato, MD,† Letizia Riva, MD,* Ornella Leone, MD,§ Mohsen Farsad, MD,† Paolo Ciliberti, MD,* Letizia Bacchi-Reggiani, MSc, MBIOSTAT,* Francesco Fallani, MD,* Angelo Branzi, MD,* Claudio Rapezzi, MD*

Bologna, Italy



ure 1. Representative examples illustrating the spectrum of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) uptake among patients

Positiv bei ATTR!!!

Perugini Score

In der Regel negativ bei AL Amyloidose!!!

Vielen Dank für Ihre Aufmerksamkeit!!